REMARKS

The Office Action of August 29, 2003 has been received and its contents carefully considered.

Claims 22 to 43 are all the claims pending in the application, prior to the present amendment.

Applicants have cancelled claim 35, have amended independent claims 36, 40 and 41 and have amended claims 37 and 39 to change their dependency so that they no longer refer to cancelled claim 35.

Claims 35-43 have been rejected under 35 U.S.C. § 102(b) as anticipated by Yu et al.

Applicants submit that Yu et al do not disclose or render obvious the present claims and, accordingly, request withdrawal of this rejection.

As discussed above, applicants have cancelled claim 35, thus leaving only claims 36 to 43 as being subject to this rejection.

The present invention, as defined in claim 36 as amended above, is directed to a drug composition comprising an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, dissolved in a solvent, wherein the solvent comprises at least one -^{17}OH in its chemical structure, and ^{17}O in the -^{17}OH exerts a relaxation effect on the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton bonded to the ^{17}O, thereby enabling detection by nuclear magnetic resonance, and a concentration of the active ingredient in the resulting drug

composition is equal to a concentration of the active ingredient in the administrative form of the medicament.

Thus, applicants have amended claim 36 to recite that the concentration of the active ingredient in the drug composition is equal to a concentration of the active ingredient in the administrative form of the medicament.

The Examiner states that Yu et al (J. Magnetic Resonance, Ser. B 102, 1993, pp. 218-221) teach the effects of ^{17}O-labeled water on the backbone amide 1H relaxation rates of the FKBP/ascomycin complex, and disclose a composition comprising FKBP, ascomycin and $H_2{}^{17}O$ as a composition containing a solvent and a drug delivery system. Further, the Examiner states that the active ingredient in the drug composition of Yu et al is equal to the concentration of the active ingredient of the medicament.

However, Yu et al are quite silent as to the fact that a drug to be contained in the composition may be detected by nuclear magnetic resonance. Indeed, the concentration of the active ingredient in the composition of Yu et al was determined for the purpose of the in vitro NMR analysis (the structural analysis by NMR) of the FKBP/ascomycin complex.

On the other hand, the concentration of the active ingredient of the present drug composition as claimed in the amended claim 36 is determined so as to be equal to the concentration of the active ingredient in the administration form of the medicament.

Accordingly, the concentration of the active ingredient is fundamentally different between the composition of Yu et al and the drug composition of the present application.

In this respect, applicants point out that the object of the present application is quite different from that of Yu et al. Yu et al is directed to a method for determining the bonding states of water molecules in proteins or DNA. Yu et al merely provide the composition disclosed in Yu et al for the purpose of the in vitro NMR analysis of the FKBP/ascomycin complex, using the shortening effect of the amide proton relaxation times by the ^{17}O nucleus. This object of Yu et al is clearly distinguishable from the object of the present application, disclosed at page 5, lines 10 to 16 of the present specification (page 5, line 23 to page 6, line 3 of the original text).

That is, the object of the present invention is to provide a physiologically acceptable medical drug which enables an external detection of the effective circulation or distribution of the drug in the target organ or tissues in vivo where it is needed, by the nuclear magnetic resonance method before or at the same time as the administration of a therapeutic agent to each patient. The concentration of the active ingredient in the present drug composition is determined by the administration form of the medicament in accordance with the above-mentioned object. In other words, the concentration of the active ingredient in the present drug composition corresponds to the concentration of the active ingredient dissolved in the solvent in solution as an administration form conventionally used.

It is clear to one of ordinary skilled in the art that the concentration of the active ingredient of the composition of Yu et al is quite different from that of the present drug composition, on the basis of the difference mentioned above.

Moreover, the Examiner states that the composition disclosed in Yu et al is able to perform the intended use of the present invention. However, the composition disclosed in Yu et

al cannot apply to the detection of the distribution of the drug to be contained in the administration form of the medicament in vivo by nuclear magnetic resonance, so that the effect of the present invention cannot be obtained by the composition disclosed in Yu et al. As is mentioned above, the aqueous solution of the FKBP/ascomycine complex disclosed in Yu et al is clearly different in the form as well as the concentration of the active ingredient from the present drug composition. Accordingly, in order to externally detect the effective circulation or distribution of the drug in the target organ or tissues in vivo by the nuclear magnetic resonance method, applicant cannot use the composition disclosed in Yu et al.

Thus, the drug compositions claimed in the amended claims 36 to 39 are clearly distinguishable from the composition disclosed in Yu et al.

Turning now to claims 40 and 41, and the claims dependent thereon, applicants have amended claims 40 and 41 to direct them to a drug composition that comprises a compound that contains the moiety $-^{33}SH$ and to no longer refer to a compound that contains the moiety $-^{14}NH$. In addition, applicants have amended claim 41 to recite that the concentration of the active ingredient in the resulting drug composition is equal to a concentration of the active ingredient in the administrative form of the medicament

Thus, the present invention as defined in claim 40 as amended above is directed to a drug composition comprising an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, dissolved in a solvent, wherein the active ingredient of the medicament contains a compound comprising $-^{33}SH$ in its chemical structure, and ^{33}S in the $-^{33}SH$ exerts a relaxation effect on

the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton bonded to the or $-^{33}S$, thereby enabling detection by nuclear magnetic resonance.

Further, the present invention as defined in claim 41 as amended above is directed to a drug composition comprising an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, dissolved in a solvent, wherein the active ingredient of the medicament contains a compound comprising $-^{33}SH$ in its chemical structure, and ^{33}S in the $-^{33}SH$ exerts a relaxation effect on the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton bonded to the ^{33}S, thereby enabling detection by nuclear magnetic resonance; and a concentration of the active ingredient in the resulting drug composition is equal to a concentration of the active ingredient in the administrative form of the medicament.

Yu et al do not refer to the $-^{33}$ SH moiety. Accordingly, applicants submit that Yu et al do not defeat the patentability of claims 40 to 43 for this reason alone.

Further, with respect to claim 41, which now recites that the concentration of the active ingredient in the resulting drug composition is equal to a concentration of the active ingredient in the administrative form of the medicament, the above arguments made with respect to claim 36 apply in a corresponding manner.

Taking this opportunity, applicants further explain the unobviousness of the present drug composition in view of Yu et al.

The Yu et al article is directed to experiments in which the T_1 and T_2 relaxation times of the backbone amide protons of FKBP are compared in the presence of ^{16}O-labeled water versus ^{17}O-labeled water. Yu et al state that based on previous studies of the DNA/drug adduct, the backbone amide protons would be expected to display a change in the relaxation rates in the presence of ^{17}O-labeled water.

Yu et al disclose on page 219 that as a result of the tests performed by Yu et al, it is clear that there were no significant selective changes in the amide ^{1}H T_1 and T_2 relaxation rates for the FKBP/ascomycin complex.

Yu et al state, at page 220, that the exchange of the backbone amide protons for the relatively fast-relaxed protons on the ^{17}O-labeled water molecule will have negligible effects on the amide ^{1}H, T_1 and T_2 relaxation rates. Yu et al state that the present results are contradictory to the earlier observation of the dramatic changes in the ^{1}H, T_1 relaxation times of the DNA/drug adduct. Yu et al state that at the present time, it is unclear why such large effects on the proton T_1 and T_2 values were previously observed.

Yu et al disclose a technique for obtaining information relating to the location of protein-bound water molecules by using the change in the H^1 NMR relaxation rates of the biomacromolecule in the presence of ^{17}O-labeled water. Yu et al merely discuss therein a basic relaxation time in the presence of ^{17}O-labeled water. Yu et al disclose that ^{17}O-labeled water does not significantly affect the T_1 and T_2 relaxation times of the NH_2 protons of protein, and

disclose that the small change in T_2 relaxation times is due to differences in the viscosity of the samples. See page 219, lines 1 to 11 of the left column.

On the other hand, the drug compositions of the present application affects T_2 relaxation time of the proton (H) by the ^{17}O (claim 36) or ^{33}S (claims 40 and 41) in the drug composition, at the time of the administration of the drug to a living body. Thus, the distribution of the present drug can be determined by imaging by using the relaxation effects exerted on the proton. Yu et al neither disclose nor suggest such phenomenon that ^{17}O and ^{33}S of the present drug affect the T_2 relaxation time of the proton (H).

Further, Yu et al disclose that the NH_2 protons of protein have exchange times on the order of minutes or longer, and disclose that the effects on the T_1 and T_2 relaxation times of NH_2 protons, due to the exchange of the NH_2 protons for the protons on the ^{17}O-labeled water, is negligible. See page 220, lines 2 to 9 of the left column.

On the other hand, as is defined in the amended claim 36, the relaxation effect spreads through the exchange of a proton in a living body for the proton of the compound carrying $-^{17}OH$ in the drug composition of the present application, and thereby the distribution of the drug enables to detect by nuclear magnetic resonance. Yu et al do not touch at all such a spread of the relaxation effect due to the exchange of a proton in a living body with the proton bonded to ^{17}O in the present drug composition.

A similar analysis applies to claims 40 and 41 with respect to the compound carrying $-^{33}SH$ in the drug composition.

Accordingly, none of the disclosures of Yu et al suggests the present application, and one of ordinary skill in the art cannot arrive at the present invention on the basis of the disclosures of Yu et al.

Turning now to the Declaration evidence that applicants submitted on April 17, 2003, the Examiner states that the unexpected results should be demonstrated in the Declaration.

However, as is mentioned in the Reply Under 37 C.F.R. § 1.114 filed June 17, 2003, applicants believe that the unexpected results of the present invention are clearly demonstrated in the Declaration filed April 17, 2003.

The present drug composition as recited in claim 36 enables the detection of the biodistribution of the drug administered along with $H_2{}^{17}O$, by nuclear magnetic resonance. The results shown in the Declaration demonstrate that the biodistribution of the $H_2{}^{17}O$ (solvent) in the present drug composition varies depending on the combination of the solvent and solute of the present drug composition. The results indicate that the biodistribution of water varies from a drug composition to a drug composition, and suggest that if the drug composition is selected so as not to be suitable for the administration form of the drug, then the biodistribution of the drug cannot be properly detected from outside of a living body before the administration of the drug to each patient.

None of the prior art references disclose or suggest that the biodistribution of water varies from a drug composition to a drug composition. The Declaration that was filed proves the above fact as an unexpected effect of the present invention.

Accordingly, applicants believe that the Declaration demonstrates the unexpected results of the present invention.

In view of the above, applicants submit that Yu et al do not disclose or render obvious the subject matter of the present claims and, accordingly, request withdrawal of this rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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